The elimination of congenital syphilis has remained an elusive goal of public health policy. Worldwide, syphilis remains a significant cause of neonatal morbidity and mortality. Its occurrence during pregnancy, especially among racial and ethnic minority populations who underutilize the health care system is associated with spontaneous abortion, stillbirth, nonimmune hydrops, preterm delivery, and perinatal death. The continued occurrence of congenital syphilis in both industrialized and developing nations highlights the need to better understand the extent of neonatal infection with Treponema pallidum and, in particular, its effect on the central nervous system (CNS).2

Although the clinical and pathologic manifestations of congenital syphilis in the CNS have been described, few reports discuss pituitary abnormalities.3–7 We report a case of a preterm infant with congenital syphilis who, at autopsy, had an evolving gumma in the anterior pituitary gland. The failure of appropriate maternal penicillin therapy during the last 4 weeks of pregnancy to treat adequately the fetal infection emphasizes the need for evaluation and treatment of these high-risk infants.

CASE REPORT

A 1236-g male infant was delivered vaginally at 26 weeks of gestation (85% weight for gestational age) to a 26-year-old gravida V, para V Latin American female. Prenatal serologic tests at 22 weeks of gestation revealed an absence of antibodies to human immunodeficiency virus, a negative hepatitis B surface antigen test, and immunity to rubella but a Venereal Disease Research Laboratory (VDRL) test titer of 1:16 with a reactive microhemagglutination assay for T pallidum antibody test. A rapid plasma reagin test that was performed 12 months earlier was nonreactive. The mother was diagnosed with early latent syphilis, and she received 2 doses of 2.4 mU of benzathine penicillin G, 10 days and 3 days before delivery. One day after her second dose of benzathine penicillin G, she developed preterm labor, and subsequently, she presented to the labor suite 4 hours before delivery. Ampicillin for group B streptococcal chemo prophylaxis and dexamethasone for promotion of lung maturation were administered 2 hours before delivery. There was no history of illicit drug use. Maternal VDRL titer at delivery was 1:16.

The infant had Apgar scores of 5 and 6 at 1 and 5 minutes, respectively. Respiratory distress developed shortly after birth, and the infant required mechanical ventilation. Physical examination revealed a hypertonic infant with a head circumference in the 40th percentile, a peeling skin rash over the extremities and trunk, a protuberant abdomen with a liver palpable 4 cm below the right costal margin, and a spleen palpable 2 cm below the left costal margin. Laboratory studies showed a hemoglobin level of 14.3 g/L; a hematocrit level of 43%; a white blood cell count of 65 (4% segmented neutrophils, 50% lymphocytes, and 1% monocytes; and a platelet count of 143. One day after her second dose of benzathine penicillin G (50 000 U/kg IV q 12 hours) was initiated because of a lumbar puncture performed, and therapy with aqueous penicillin G (50 000 U/kg IV q 12 hours) was initiated because of a presumptive diagnosis of congenital syphilis. The cerebrospinal fluid (CSF) examination showed a VDRL titer of 1:32, a white blood cell count of 65 (4% segmented neutrophils, 50% lymphocytes, 43% monocytes, 1% eosinophils, 1% basophils, and 1%
atypical lymphocytes), a red blood cell count of 55, and glucose and protein concentrations of 34 mg/dL and 767 mg/dL, respectively. Urine culture for cytomegalovirus was sterile. Cytogenetic analysis revealed a normal male karyotype.

Chest radiograph (Fig 1) was consistent with pneumonitis. Cranial ultrasound revealed moderate ventriculomegaly with a slightly enlarged fourth ventricle but no evidence of intraventricular hemorrhage (Fig 2). Long bone radiographs showed osteochondritis of both upper and lower extremities, consistent with a diagnosis of congenital syphilis. Because of the abnormal neurological examination, cerebral abnormalities, and continued respiratory deterioration, the infant was removed from life support, and subsequently, he died on the third day of life.

Consent for an autopsy was granted by the parents. The findings were consistent with the diagnosis of congenital syphilis. The placenta weighed 618 g (>90th percentile). The triad of focal villitis with mononuclear infiltration, vascular abnormalities consisting of endothelial proliferation and perivascular fibrosis and inflammation, and immature villi were characteristic of syphilis. In addition, there was neutrophilic infiltration of the chorion and amnion with focal microabscesses suggestive of acute chorioamnionitis.

The pancreas, spleen, thymus, lungs, kidneys, and testes demonstrated lymphocytic infiltration with extensive fibrosis in the pancreas, capsule of the spleen, and interstitium of the thymus. There was prominent extramedullary hematopoiesis in the portal areas of the liver with focal subcapsular fibrosis and giant cell transformation. The tibiae and femora displayed reactive periostitis of the metaphyses with thickening of the cortex and irregularity of the growth zone. Steiner staining of the liver, spleen, pancreas, tibia, and femur demonstrated no spirochetes.

Macroscopic examination of the brain revealed yellow cloudy CSF and enlarged lateral ventricles. Microscopically, there was lymphocytic infiltration of the leptomeninges and of the walls of the cerebral vessels. A friable yellow mass extended from the anterior pituitary gland under the optic chiasm and into the anterior sella turcica (Fig 3). This mass was comprised of necrotic debris and degenerating neutrophils. Steiner stain of this lesion demonstrated numerous spirochetes; this was consistent with an evolving gumma of the anterior pituitary gland (Fig 4). There also

Fig 1. Chest radiograph of infant showing increased interstitial markings consistent with pneumonitis. Note osteochondritis affecting the iliac crest.

Fig 2. Moderate ventriculomegaly seen on cranial ultrasound.

Fig 3. Gross photograph of base of skull shows pituitary gland and evolving syphilitic gumma. A indicates the anterior fossa; P indicates the posterior fossa; → indicates the anterior pituitary; ▲ indicates the optic nerves; and the star indicates the evolving pituitary gumma.

was lymphocytic and plasma cell infiltration with fibrosis in the meninges overlying the pituitary gland. In addition, the frontoparietal area of the brain as well as the temporal lobes and basis pontis showed extensive neuronal and white matter loss with intense gliosis, microcystic change, and infiltration by macrophages. These changes were consistent with extensive hypoxic/ischemic encephalopathy.

The infant’s serum and CSF were tested for immunoglobulin M (IgM) antibodies against specific *T. pallidum* antigens by immunoblotting as previously described. IgM antibody directed against the 47-kd antigen of *T. pallidum* was detected in both serum and CSF. The infant’s endotracheal aspirate, blood, and CSF, which was obtained from the lumbar puncture as well as at autopsy, were tested by polymerase chain reaction (PCR) for specific *T. pallidum* DNA as previously described. Rabbit infectivity testing (RIT) of the infant’s blood and lumbar CSF was performed as previously described. Both PCR and RIT of the clinical specimens
were performed after the infant had received 2 doses of ampicillin; PCR of CSF obtained at autopsy was performed after 3 days of penicillin therapy. PCR of blood and lumbar CSF was negative, although PCR of endotracheal aspirate and CSF from autopsy was positive. RIT of blood and CSF failed to detect spirochetes.

**DISCUSSION**

This case of congenital syphilis highlights the clinical manifestations and extensive organ destruction that can accompany treponemal infection. In addition, it describes the unusual finding of an evolving gumma of the pituitary gland in a newborn. Involvement of the pituitary gland in congenital syphilis typically consists of interstitial inflammation and fibrosis of the anterior lobe and, less commonly, mililiary gummas, whereas the neurohypophysis usually remains intact. In a review of gummas of the hypothalamus, Fink cited Simmonds who, in 1914, found pituitary changes at autopsy in 5 of 12 (42%) infants with congenital syphilis. In 1971, Oppenheimer and Hardy reported hypophysial abnormalities in 5 (38%) of 13 cases of congenital syphilis, with the anterior lobe showing typical interstitial inflammation and fibrosis but no gummas. In a subsequent review of 432 autopsies of infants and fetuses with congenital syphilis, Oppenheimer and Dahms described “abscess-like necrosis” in various organs including the adenohipophysis. The incidence of hypophysial disease was not noted. They considered these lesions to be similar to the suppurrative inflammation that occurs within dilated thymic Hassle’s corpuscles in some patients with congenital syphilis known as Dubois’ abscesses. However, the comparison of the destructive extrathyemic lesions seen in the current case to intracorpuscular Dubois’ abscesses seems tenuous. Although it is true that gummas in adult tertiary syphilis contain only rare treponemes and lack suppuration, the evolution of lesions in congenital syphilis does not mimic exactly the evolution of syphilitic disease in adults. It is more likely that large areas of suppurrative necrosis with peripheral fibrosis and the numerous spirochetes found in congenital syphilis represent an evolving form of gumma unique to congenital disease. In contrast to the pituitary gland, syphilitic abnormalities involving the brain or meninges are uncommon in autopsy cases, although CNS invasion by T. pallidum occurs in the majority of infants who have clinical, laboratory, and/or radiographic abnormalities of congenital syphilis. Because hypophysal involvement occurs more commonly in autopsy cases, it may be that the majority of infants with CNS invasion survive their infection, whereas hypophysal invasion represents a more significant disease resulting in death.

In 1993, Daaboul et al described 2 infants who had reactive serum and CSF VDRL tests and who presented with hypoglycemia and were later diagnosed with hypopituitarism. Of the 2 infants, 1 died at ~2 months of age secondary to necrotizing enterocolitis and was found to have almost total effacement of the anterior pituitary lobe by fibrosis. Pituitary function was not evaluated in our patient; however, he never experienced alterations in glucose homeostasis. It is likely that if he had survived, the extensive destruction of the anterior pituitary gland that was present at autopsy would have resulted in pituitary dysfunction. Therefore, evaluation of pituitary function is recommended in infants with congenital syphilis who manifest persistent hypoglycemia and/or abnormal growth.

This case also addresses important issues concerning the treatment of mothers with syphilis during pregnancy and the risk of fetal infection. Maternal penicillin treatment during pregnancy is considered adequate fetal therapy in the majority of cases. However, as many as 14% of pregnant women who are adequately treated with penicillin will have fetal demise or deliver infants with clinical evidence of congenital syphilis. The majority of these women were treated for secondary syphilis, and this stage is associated with a high degree of spirochetemia leading to placental and fetal infection. A second dose of benzathine penicillin G administered 1 week after the initial dose has been recommended by some authorities for treatment of early syphilis during pregnancy to minimize the risk of fetal treatment failure. The mother of our patient received 2 weekly injections of benzathine penicillin G before delivery, and at autopsy there were no spirochetes detected in placental tissue or non-CNS organs. However, it was not sufficient to treat effectively an established fetal infection of the CNS, and it has been suggested that the CNS may represent a sequestered site for persistence of treponemal infection despite the administration of systemic penicillin therapy.

Concern has been raised as to the adequacy of maternal treatment for syphilis during the final 4 weeks of pregnancy to prevent or treat fetal infection. The majority of fetal treatment failures have occurred when maternal treatment was provided late in gestation. It may be that the increases in renal clearance and plasma volume that occur as pregnancy progresses result in lower serum and CSF penicillin concentrations in both the mother and fetus. Moreover, when maternal treatment occurs late.
in gestation (ie, during the last 4 weeks of pregnancy), there may not be sufficient time for the fetus to be treated adequately. However, it is also clear that the clinical, laboratory, and radiographic abnormalities seen in infants with congenital syphilis take several months to resolve and that their presence may not be indicative of active infection in the newborn. The visualization of spirochetes in the pituitary gland in our patient along with a positive PCR performed on CSF obtained at autopsy support ongoing infection. This is also supported by the infant’s umbilical cord VDRL titer, which was fourfold greater than was the maternal titer at delivery. We also detected IgM antibody directed against specific T pallidum antigens in this patient’s serum and CSF, and these findings support the diagnosis of congenital syphilis, because IgM antibody is unable to cross the placenta.2 We were unable to detect either the organism or T pallidum DNA in blood and CSF. This was most likely attributable to the fact that both the mother and infant received antimicrobial therapy before the clinical specimens were obtained. These results support our previous findings that a positive IgM immunoblot may be the only marker of fetal infection with T pallidum.

Pneumonia alba, a focal obliterator fibrotic lesion consisting of interstitial scarring and thickening of the alveolar walls with loss of alveolar spaces, is the classic pulmonary lesion seen at autopsy in the lungs of infants with congenital syphilis. It typically has a roentgenographic appearance of complete opacification of the lung fields. In our patient, chest radiograph showed bilateral haziness of the lung fields and increased interstitial markings. The clinical course was suggestive of pneumonia and T pallidum DNA was detected in the endotracheal aspirate by PCR, supporting the role of T pallidum in causing the roentgenographic abnormalities. This was also confirmed at autopsy by the finding of an interstitial lymphocytic infiltrate in the lungs that was consistent with pneumonia.

CONCLUSION

In summary, this case highlights some of the major clinical and pathologic findings seen in early congenital syphilis, while focusing on the rare autopsy finding of an evolving gumma in the pituitary gland of a newborn. Furthermore, it documents the failure of maternal syphilis treatment during the last 4 weeks of pregnancy to cure fetal infection. This failure was demonstrated by the abnormal physical examination of the infant at birth, an infant VDRL titer that was fourfold greater than was the maternal titer, the finding of spirochetes in the anterior pituitary gland, a positive PCR of CSF obtained at autopsy, and a positive serum IgM immunoblot. This case supports the recommendation from the Centers for Disease Control and Prevention and the American Academy of Pediatrics that all infants born to mothers with syphilis treated during the last 4 weeks of pregnancy should receive penicillin therapy.14,15

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